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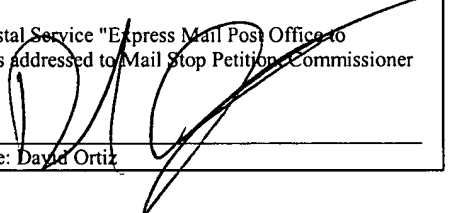
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Michel Franz	Examiner:	Thurman K. Page
Serial No.:	10/789174	Group Art Unit:	1615
Filed:	February 26, 2004	Docket No.:	09997.0057USU1
Title:	STABILISED PHARMACEUTICAL COMPOSITION COMPRISING AN EXTENDED RELEASE NON-STEROIDAL ANTI-INFLAMMATORY AGENT AND AN IMMEDIATE RELEASE PROSTAGLANDIN		

CERTIFICATE UNDER 37 CFR 1.10:
"Express Mail" mailing label number: EV 495845505 US
Date of Deposit: May 27, 2005

I hereby certify that this paper or fee is being deposited with the U.S. Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: 
Name: David Ortiz

PETITION TO MAKE SPECIAL UNDER 37 C.F.R. § 1.102(C)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. § 1.102(c), Applicants hereby petition the Commissioner to make the above-identified application special so that it may be taken out of turn for immediate action. The grounds and conditions for granting the application special are found in the Manual of Patent Examining Procedure (Edition 8, August 2001, revised February 2003), § 708.02 VIII entitled "Special Examining Procedure for Certain New Applications - Accelerated Examination."

In accordance with Manual of Patent Examining Procedure § 708.02 VIII, Applicants:

- A) Enclose the petition fee set forth in 37 C.F.R. 1.17(h);
- B) Submit the pending claims are directed to a single invention and do not require restriction to a single invention. If the Office determines the claims are not obviously directed to a single invention, Applicants will make an election without traverse as a prerequisite to the grant of special status;

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C) Enclose a copy of a European Search Report for the above-referenced application including the fields of classification searched;

D) Enclose one copy of each of the references deemed most closely related to the subject matter encompassed by the claims, including the references cited in the European Search Report; and

E) Submit an accompanying detailed discussion of the references that points out how the claimed subject matter is patentable over the references.

Pending Claims

1. (original) A solid pharmaceutical composition offering a dual release and comprising at least two separate regions,
 - a first region comprising at least one non-steroidal anti-inflammatory drug (NSAID) and an adequate pharmaceutical carrier containing a retardant material for an extended release delivery of said non-steroidal anti-inflammatory drug (NSAID), and
 - a second region comprising a stabilized gastroprotective prostaglandin and an adequate pharmaceutical carrier for an immediate release of said stabilized gastroprotective prostaglandin.
2. (original) The pharmaceutical composition according to claim 1, wherein the first and the second regions are separated by a third region.
3. (previously amended) The pharmaceutical composition according claim 1, wherein the non-steroidal anti-inflammatory drug (NSAID) is selected from the group consisting of aceclofenac, diclofenac, diflunisal, fenbufen, flufenamic acid, ibuprofen, indomethacin, ketoprofen, meclofenamate sodium, meloxicam, mefenamic acid, nabumetone, naproxen, piroxicam, suprofen, tiaprofenic acid, acetylsalicylic acid, flurbiprofen, ketorolac, oxaprozin, sulindac, tenoxicam, tiaprofenic acid and suitable salts, esters, amides, prodrugs or analogues thereof.
4. (previously amended) The pharmaceutical composition according to claim 1, wherein the retardant material of the first region is selected from the group consisting of lipidic materials, acrylic and methacrylic acid polymers and copolymers, cellulose-based polymers and a mixture thereof.
5. (previously amended) The pharmaceutical composition according to claim 1, wherein the prostaglandin is a "E-series" prostaglandin selected from the group consisting of PGE1, PGE2, misoprostol, enoprostol, enisoprost, rosaprostol, miraprostol and analogues or derivatives thereof.
6. (original) The pharmaceutical composition according to the claim 5, wherein the gastroprotective prostaglandin is misoprostol stabilized by a dispersion in hydroxypropylmethylcellulose (HPMC) or polyvinylpyrrolidone (PVP).

7. (previously amended) The pharmaceutical composition according to claim 1, which has a core tablet format comprising:

- a first region being a core containing a therapeutically effective amount of NSAID and a retardant material for an extended release delivery of the NSAID and,
- a second region being a mantle dry coating surrounding the core containing a therapeutically effective amount of a stabilized gastroprotective prostaglandin and a pharmaceutical carrier for an immediate release of said stabilized gastroprotective prostaglandin.

8. (previously amended) The pharmaceutical composition according to claim 1, which has a layered – or multilayered tablet format comprising:

- a first region being a first layer containing a therapeutically effective amount of NSAID and a retardant material for an extended release delivery of the NSAID and,
- a second region being a second layer containing a therapeutically effective amount of stabilized gastroprotective prostaglandin and a pharmaceutical carrier for an immediate release of said gastroprotective prostaglandin and, optionally
- a third region being a third layer containing no active ingredient and separating the first and the second layers.

9. (previously amended) The pharmaceutical composition according to claim 1, which has a multiple units tablet format comprising:

- a first region made of several units containing a therapeutically effective amount of NSAID and a retardant material for an extended release delivery of NSAID and,
- a second region made of a powder of one or several units containing a therapeutically effective amount of stabilized gastroprotective prostaglandin and a pharmaceutical carrier for an immediate release said stabilized gastroprotective prostaglandin.

10. (previously amended) The pharmaceutical composition according to claim 1, which has a capsule format, preferably made of the Hydroxypropylmethylcellulose (HPMC) polymer and comprising:

- a first region made of one or several units containing a therapeutically effective amount of NSAID and a retardant material for an extended release delivery of NSAID and,
- a second region made of a powder of one or several units containing a therapeutically effective amount of stabilized gastroprotective prostaglandin and a pharmaceutical carrier for an immediate release of said of stabilized gastroprotective prostaglandin.

11. (previously amended) The pharmaceutical composition according to claim 1, wherein the non-steroidal anti-inflammatory drug (NSAID) is diclofenac, ketoprofen or naproxen and the stabilized gastroprotective prostaglandin is a stabilized misoprostol.

12. (previously amended) A method for the treatment and/or the prevention of inflammatory conditions or diseases in a mammal patient, including the human, that comprises the step of administering a sufficient amount of the pharmaceutical composition according to claim 1, to said mammal patient.

13. (original) The method according to claim 12, wherein said inflammatory condition or disease is osteoarthritis or rheumatoid arthritis.

14. (previously amended) The method of claim 12, wherein the pharmaceutical composition is administrated as dual release formulation allowing a one a day or twice a day dosing into humans.

15. (previously amended) A packaging to minimize oxygen permeation, comprising the pharmaceutical composition according to claim 1 and an additional gastroprotective drug analogue medicament.

Remarks

The European Search Report and cited references are presented in a supplemental information disclosure statement accompanying this petition. The corresponding European application, Application No. EP 04447005, with the claims as searched is provided as Appendix A to this petition. The European Application with claims is provided to show the searched European claims are of the same or similar scope to the claims in this U. S. Application for which special status is requested.

Applicant's detailed discussion of the references that points out how the claimed subject matter is patentable over the references is provided below. Additional supporting information is provided as seven annexes to this petition. The documents provided as annexes are also supplied with the supplemental disclosure statement.

Documents of the state of the art cited in the search report of the European Patent Application EP 04447005.2 published as No. EP 1462098

The search report of the European Patent Office has cited four documents of the state of the art, two documents cited in the category x and two documents cited in category A against the client invention.

X	US 2002/05498
D,P,	US 6,537,582
A	US 6,312,724
A	WO 02/22108

1) US 2002/05498 corresponding to US 6537582B1

The relevant paragraphs of this document are paragraphs 1, 2 and 6 to 11 and 27 in combination with the content of the claims and the content of the examples. References below are to patent publication, US 2002/05498, which also corresponds to US 6537582B1.

A. The cited prior art describes a delayed release mechanism

Various paragraphs of the prior art document specification describe that the scope of the described composition is limited to an oral formulation dosage that includes a mixture of delayed release formulation of NSAIDS and an mixture of one or more excipients and a prostaglandin (see paragraphs [0006] and [0007] and second sentence of paragraph [0011]).

Furthermore, this document provides an example of such delayed response in the paragraph [0049]: dissolution properties of the composition for obtaining delayed release (dissolution properties were determined by exposure to an acid medium for two hours, followed by a measurement of dissolution in alkaline buffer).

These characteristics correspond to the definition of diclofenacsodium delayed release (enteric coated) tablets as proposed in the United States Pharmacopeia (USP) since a long time, especially in edition XXV (pages 554-555) (See annex 1 and supplemental IDS).

According to the USP document, such delayed release is obtained for a galenic form that releases only a very small portion of the active compound when maintained in acidic medium for two hours and that releases at least 75% of the active compound after 45 minutes at a pH 6.8 (artificial intestinal medium).

A comparative definition of delayed and sustained (or prolonged) release is present in the (p 170) of European Directive 75/318/EEC, provided as annex 2 and in the supplemental IDS.

Therefore, the teaching of the delayed release obtained in this cited prior art corresponds to a delayed release described in the scientific and nomenclature literature requiring enteric coating formulations.

B. The cited prior art describes enteric coating formulations

All the coating of the prior art (US2002/0054908) are based on excipients leading to enteric coating only.

If we refer to the Handbook of Pharmaceutical Excipients (**HBE**) (See annex 3 and the supplemental IDS), the described coating agent in the cited prior art examples correspond to enteric coating only.

Polymethacrylates / Eudragits formulation

The paragraphs [0022], [0023] and [0038] describe Eudragits L30D-55 formulations and the paragraph [0024] describes Eudragits L and S formulations. According to the Handbook of Pharmaceutical Excipients (HBE) (see table 2, page 464) such coating agents are used for enteric coating only.

Hydroxypropyl methylcellulose phthalate (hypromellose phthalate or HPMCP

This excipient, as well as other phthalates, described in paragraph [0024] is used for enteric coating only (see also page 301 of HBE). The phthalates dissolve when the dosage form reaches the higher pH of the intestine.

Plasticizer

The claim 18 and the last sentence of paragraph [0024] describe the use of a plasticizer that is required for an enteric coating. Such plasticizer is usually not required for extended release formulations.

Hydroxypropyl Methylcellulose (hypromellose or HPMC) formulation

This type of excipient is described in paragraph [0022], but this example does not suggest the use of this excipient is to create the enteric coating.

C. The cited prior art is a teach-away document for the use of sustained release preparations

In the paragraph [0004], the inventors of the US patent application US 2002/0054908 mention the increased use of sustained (or extended) release preparations of NSAIDS drugs to reduce the number of doses for each day that are required by the patient.

Furthermore, the drawbacks of such preparations are mentioned in paragraph [0004]. Furthermore, the paragraph [0005] stated that the incorporation of misoprostol into such products (this definition seems to apply also to a sustained release preparation as described in paragraph [0004]) has not been disclosed previously.

For these reasons, the cited prior art document clearly teaches away from the scope of the client invention.

Furthermore, the terms "sustained release preparations" are only described as a prior art formulations. Said specific formulation, well known from the inventors, is not mentioned elsewhere in the description of US patent application 2002/0054908. Therefore, the terms used in the paragraphs [0010] and [0011] do not refer to sustained release formulations.

For this reason, the cited prior art document clearly teaches away from the scope of the client invention.

D. Interpretation of paragraphs [0010] and [0011]

The paragraph [0010] refers to beads or granules having coatings adapted to provide programmed (or modified) release according to the position in or along the gastro-intestinal track.

The paragraph [0011] mentions that the use of either a single slowly erodible coat or differing levels or types of coating are adapted to provide a continuous or distributed release profile through the gastro-intestinal track. However, the second sentence of paragraph [0011] again refers to an (obtained) delay(ed release), which is dependent on the pH of the gastro-intestinal track.

It is important to know that this prior art does not propose a definition of the terms "continued" or "distributed release profile".

Furthermore, the teaching of the paragraphs [0010] and [0011] seems to refer to "traditional" enteric coating formulations that allow only a "delay(ed)" release of NSAIDS in specific portion(s) of the gastro-intestinal track (in the intestine).

The description of paragraphs [0010] and [0011] seems to clearly correspond to the traditional drug release of an enteric coating that provides a modified or a programmed release in the intestine: that may result in a continuous (and complete) release in the intestine only or may result in a distributed release along the intestine track.

Therefore, it appears that paragraphs [0010] and [0011] of the cited document US 2002/0054908 do not correspond to the sustained (or extended) formulation of our client invention.

E. Non enabling disclosure of paragraph [0010] or [0011]

The enteric coating described in this prior art document is applied on particles of a very small size, preferably between 300 and 500 μm , as mentioned in [0022]. However, these paragraphs do not describe examples of coating that could be used in these formulations and any coating of such beads or granules of such small size does not guarantee that a sustained release (in the intestine) will be obtained.

Therefore, it is highly possible that, instead of the resulting of a hypothetical and non-exemplified "sustained" release of the active product in the intestine, the result obtainable with a

coating upon these small size beads or granules is an at random and discontinuous release of the active compound in different portions of the intestine.

Thus the paragraphs [0010] and [0011] do not provide a disclosure of formulations, which could obviously result in any efficient definition release mechanism that could correspond to a sustained release in the intestine.

F. Sustained, extended or prolonged release (versus delay(ed) definitions

The scope of the client invention differs from this cited prior art document by the use of a sustained or extended release preparation.

The composition according to the client invention presents characteristic features that differ from an enteric coating resulting in delayed release as described in this prior art document. The cited prior art (US 2002/0054908) clearly mentions in paragraphs [0004] and [0005] that sustained release preparation corresponds to compositions of prior art, which differ from the claimed composition.

Furthermore, the client patent application clearly mentions the difference between enteric coatings of prior art and the client extended release formulations. Enteric coatings are described as prior art in the paragraphs [0005] of the client patent application. The drawbacks of such prior art composition are also described in said paragraph.

The definition of a sustained or extended release is also described in paragraph [0006] and [0009] of the client patent application.

In particular, the paragraph [0009] of the client patent application refers to diclofenac sodium extended release tablet monograph published by the US Pharmacopeia. Said document (Pharmacopeial Previews) is presented in the enclosed annex 4 and the supplemental IDS.

A more recent publication of the US Pharmacopeia, which describes in detail the characteristics of the dissolution tests for the diclofenac sodium monograph, is present in the enclosed annex 5. These dissolution tests correspond to the figures 1 and 2 of the client invention (see annex 6).

Finally, the inventor provides hereafter documents obtained from the website of Novartis showing that extended or sustained release formulation finds a clear definition in the prior art and is usually identified by the abbreviation "ER" or "XR" (as mentioned in the client patent application, on paragraph [0006]).

Therefore, extended or sustained release formulations find clear definition in the prior art and in the client patent application.

These additional prior art documents (annexes 4 and 5) clearly show that an extended or prolonged release system presents a specific dissolution test profile.

It is important to compare these publications (annexes 4 and 5) to a diclofenac sodium delayed release tablet formulation present in the enclosed annex 1 (these data should also be compared to dissolution curves of annex 6).

2) US patent 5601843

This US patent describes pharmaceutical tablet compositions comprising a core consisting of a therapeutically effective amount of non-steroidal anti-inflammatory agents selected from diclofenac and piroxicam and a mantle coating surrounding the core comprising a therapeutically effective amount of misoprostol. Preferably, this pharmaceutical tablet composition further comprises an intermediate enteric coating surrounding the core.

The example 1 of this US patent describes a pharmaceutically tablet composition consisting of diclofenac sodium central core and misoprostol mantle.

Therefore, such composition corresponds to an immediate release composition.

The examples 2 to 8 of this US patent describe similar compositions furthermore comprising an enteric coating of the central core.

However, these examples 2 to 8 describe tablets wherein a gastric resistance coating is put over diclofenac or piroxicam to reduce further gastric erosion due to the release in the stomach of non-steroidal anti-inflammatory drugs.

Therefore, this US patent provides neither a teaching, nor a suggestion for the preparation of sustained (or extended) release preparations non-steroidal anti-inflammatory drugs.

3) US patent 6312724

This US patent describes a sustained release composition and method for making such compositions of diclofenac and pharmaceutically acceptable salt.

However, this patent neither teaches nor suggests adding a region (or portion) comprising a stabilized gastroprotective prostaglandin and an adequate pharmaceutical carrier to this composition for obtaining an immediate release of this stabilized gastroprotective prostaglandin.

4) International patent application WO 02/22108

This international patent application describes a pharmaceutical composition comprising a non-steroidal anti-inflammatory drugs and a proton pump inhibitor, in order to reduce gastric side effect of non-steroidal anti-inflammatory drugs.

However, there is no teaching or suggestion in this patent application for obtaining the specific pharmaceutical composition according to the invention which further comprises a region (or portion) comprising a stabilized gastroprotective prostaglandin and an adequate pharmaceutical carrier for an immediate release of the stabilized gastroprotective prostaglandin.

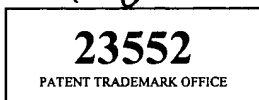
In view of the above, Applicants request that this Petition to Make Special be granted and the examination of the application be advanced.

Respectfully submitted,

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Date:

May 27, 2005



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